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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,874	11/14/2002	Jasmid Tanha	11054-1	8696

25277 7590 06/02/2004

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EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 06/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,874	TANHA ET AL.	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/22/2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *10-24 and 31-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 25-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Claims 1-40 are pending.

2. Applicant's election with traverse of Group I, claims 1-9 and 25-30 in the paper filed 3/22/2004 is acknowledged. The traversal is on the grounds that the cited reference teaches "immunized" VHH libraries, not naïve VHH libraries and it would not have been obvious to produce naïve libraries based on the cited art. This is not found persuasive because Casterman et al teach phage display libraries of immunoglobulins devoid of a light chain polypeptide (i.e., VHH) without a previous immunization of Camelid mammals (i.e., lama) (see page 24, lines 15-16). Therefore, the special technical feature recited in claim 1 is not special. Accordingly, the restricted groups set forth in the Office Action mailed 1/21/2004 are not so linked as to form a single general concept under PCT Rule 13.1. Further, the Examiner notes that rejoinder of claims will be considered once allowable subject matter has been identified in the claims currently under examination. For these reasons the restriction requirement is deemed to be proper and is made FINAL

3. Claims 10-24 and 31-40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

4. Claims 1-9 and 25-30 are under examination.

Specification

5. The disclosure is objected to because of the following informalities:

The Krebber et al reference at page 12, line 25, lists the page range for the article as "277-331", which is incorrect. The pages of the Krebber et al reference are 227-231.

Appropriate correction is required.

Claim Objections

6. Claim 8 is objected to because of the following informalities:

Claim 8 recites "absence of a tetracycline", which is not proper. Consider revising with "absence of tetracycline".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claims1-9 and 25-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-9 are indefinite for reciting "derived" in claims 1 and 4. The term "derived" is not one, which has a universally accepted meaning in the art nor is it one which has been adequately defined in the specification. The primary deficiency in the

use of this term is the absence of an ascertainable meaning for said term. Since it is unclear how the antigen-binding fragments are to be "derived" or how the llama antibodies are to be "derived" from a non-immunized llama to yield the class of derivatives referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of antibodies to said term. Further, since the term "derived" does not appear to be clearly defined in the specification, and the term can encompasses antibodies with amino acid substitutions, insertions, or deletions, antibody fragments, chemically derivatized molecules, or even antibody mimetics. In the absence of a single defined art recognized meaning for the term "derived" and lacking a definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claims.

b. Claims 7-9 are indefinite for reciting of "modified" in claim 7 because the claims fail to state the function, which is to be achieved. The term "modified" is relative in nature, which renders the claims indefinite. The term "modified" is not defined by the claims; the specification does not provide a standard for ascertaining the direction, requisite degree or endpoint, and one of ordinary skill in the art would not reasonably be apprised of the metes and bounds of the invention.

c. Claims 25-30 are indefinite for reciting "reverse-transcribing and amplifying RNA" in claim 25. It is unclear what is contemplated by the phrase "reverse-transcribing and amplifying RNA" because reverse transcription is a chemical reaction resulting in the synthesis of a cDNA molecule from an RNA template. Is the RNA reverse-transcribed and the cDNA amplified? This rejection may be obviated by amending part

(c) of claim 25 to recite "reverse-transcribing the RNA and amplifying the cDNA sequences coding for the antigen-binding fragments;".

d. Claim 7 recites the limitation "the phage vector". There is insufficient antecedent basis for this limitation in the claim. Base claim 4, form which claim 7 depends does not recite any phage vector.

e. Claim 25, step (d) recites the limitation "the amplified cDNA". There is insufficient antecedent basis for this limitation in the claim. Step (c) in claim 25 recites amplifying RNA. Further, the phrase "amplified cDNA" is not recited in the claims prior to step (d) of claim 25.

f. Claim 29 recites the limitation "the vector". There is insufficient antecedent basis for this limitation in the claim. Base claim 28, form which claim 29 depends does not recite any vector.

g. Claims 5-6 are indefinite for reciting "10^{9}" and "10^{8}", respectively. Does "10^{9}" and "10^{8}" represent the number of plaque forming units (i.e., pfu) in the phage display library or do the numbers "10^{9}" and "10^{8}" represent something else?

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 1-4 and 25-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Casterman et al (WO 94/04678, 3/3/1994).

The claims are interpreted as being drawn to a phage display library of llama antigen-binding antibody fragments obtained form a non-immunized llama comprising at least part of a VHH domain or a complete VHH domain. The claims are also drawn to a cDNA library comprising nucleotide sequences encoding antigen-binding antibody fragments comprising at least part of a llama VHH domain or a complete llama VHH domain, wherein the cDNA is obtained by isolating lymphocytes from a non-immunized llama, isolating total RNA from the lymphocytes, reverse-transcribing and amplifying the cDNA sequences encoding the antigen-binding antibody fragments, cloning the amplified cDNA into a filamentous bacteriophage vector and recovering the obtained clones. Due to the indefinite nature of claim 25 (see 112, 2nd part e above), part (d) of claim 25 is interpreted to mean that the reverse transcribed cDNA is amplified.

Caterman et al teach immunoglobulins devoid of light polypeptide chains (i.e., VHH), which include lama antibodies and the antibodies can be expressed by phage or bacteriophage (see claims 1-2, 36 and page 9, in particular). Casterman et al teach that the immunoglobulins devoid of light polypeptide chains are obtained at the level of the non-rearranged VHH repertoire using DNA from an arbitrarily chosen tissue or cell type

or at the level of the rearranged VHH repertoire of a healthy Camelid (i.e., lama), using DNA obtained from B lymphocytes (see page 19, lines 24-28 and page 21, lines 11-15 and claim 2, in particular). Further, Casterman et al teach "The preparation of antibodies can also be performed without a previous immunization of Camelids." (see page 24, lines 15-16, in particular). In addition, Casterman et al teach a cDNA library encoding a VHH obtained by (1) isolating lymphocytes from a biological sample from a Camelid (i.e., lama) without previous immunization (see page 24, in particular), (2) isolating poly A RNA from the lymphoid cells; it is inherent that poly A RNA isolation is subsequent to the isolation of total RNA, (3) synthesizing cDNA using reverse-transcriptase, (4) amplifying the cDNA, (5) cloning the amplified sequence into a vector, and (6) recovering the clones (see page 21 and claim 38, in particular). Casterman et al teach filamentous bacteriophage vectors for cloning VHH antibodies (see page 24, in particular) and the VHH domains are "complete" since the are amplified with PCR primers in the promoter, leader or framework sequences for the 5' primer and the 3' primer is located in the hinge, CH2, CH3 or the 3' untranslated region or polyA tail (see page 20, lines 5-13, in particular). For this rejection "comprising" is interpreted as open language meaning that the claims encompass additional elements including the isolation of poly A RNA, subsequent to the isolation of total RNA. Therefore, Casterman et al anticipate the claims.

11. Claims 1-4 and 25-29 are rejected under 35 U.S.C. 102(e) as being anticipated by Frenken et al [a] (U.S. Patent 6,399,763 B1, filed 1/19/2000).

The claims and their interpretation have been described supra (see item #10 above).

Claim 29 is drawn to a filamentous bacteriophage vector, which comprises the amplified cDNA sequences, which encode the antigen-binding antibody fragments from a non-immunized llama.

Frenken et al [a] teach a phage display library of antigen-binding antibody fragments comprising at least part of a heavy chain variable domain naturally devoid of light chains (i.e., VHH) obtained from a non-immunized lama (see abstract and column 6). Frenken et al teach 'full-length' VHH fragments, which are reasonably interpreted to be "complete" VHH domains (see column 5, lines 18-19 and Figure 1I, in particular). Frenken et al [a] also teach a cDNA library comprising nucleotide sequences cloned from a non-immunized lama, each nucleic acid encoding at least a part of a VHH antibody (see examples 1-3, in particular). Frenken et al [a] teach that the library of unimmunized lama antigen-binding antibody fragments are obtained by the steps comprising (1) isolating lymphocytes from a biological sample obtained form a non-immunized lama (see column 9, lines 63-66, in particular), (2) total RNA was isolated from the lymphocytes (see column 5, lines 66-67, in particular), (3) performing first-strand cDNA synthesis (i.e., reverse-transcribing) and DNA encoding VHH fragments (i.e., cDNA) were amplified by PCR (see column 10, lines 4-5, in particular), (4) cloning the amplified VHH fragments into a vector (see column 10, lines 51-52, in particular), and (5) recovering the obtained clones (see column 10, lines 62-65 and Examples 2-3,

in particular). Frenken et al [a] teach filamentous bacteriophage vectors (see column 8, lines 55-58, in particular). Thus, Frenken et al [a] anticipate the claims.

12. Claims 1-4 and 25-29 are rejected under 35 U.S.C. 102(a) as being anticipated by Frenken et al [b] (WO 99/37681, 7/29/1999).

The claims and their interpretation have been described supra (see item #'s 10 and 11 above).

Frenken et al [b] teach a phage display library of antigen-binding antibody fragments comprising at least part of a heavy chain variable domain naturally devoid of light chains (i.e., VHH) obtained from a non-immunized lama (see pages 6-7 and page 12, lines 4-13, in particular). Frenken et al [b] teach "complete" VHH domains (see Figure 1b and 1c, in particular). Frenken et al [b] also teach a cDNA library comprising nucleotide sequences cloned from a non-immunized lama, each nucleic acid encoding at least a part of a VHH antibody (see examples 1-3, in particular). Frenken et al [b] teach that the library of a non-immunized lama antigen-binding antibody fragments are obtained by the steps comprising (1) isolating lymphocytes from a biological sample obtained form a non-immunized lama (see page 13, lines 6-8, in particular), (2) total RNA was isolated from the lymphocytes (see page 13, lines 9-10, in particular), (3) performing first-strand cDNA synthesis (i.e., reverse-transcribing) and DNA encoding VHH fragments (i.e., cDNA) were amplified by PCR (see page 13, lines 11-14, in particular), (4) cloning the amplified VHH fragments into a vector (see pages 14, lines 26-28, in particular), and (5) recovering the obtained clones (see pages 14-15 and

Examples 2-3, in particular) (see also pages 10-12 for above steps). Frenken et al [b] teach filamentous bacteriophage vectors (see page 11, lines 7-8, in particular). Thus, Frenken et al [b] anticipate the claims.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-9 and 25-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Casterman et al (WO 94/04678, 3/3/1994) in view of McCafferty et al (U.S. Patent 6,172,197 B1, filed 6/7/1995) and Krebber et al (FEBS Letters, 377:227-231, 1995).

The claims are interpreted as drawn to a phage display library of antigen-binding antibody fragments obtained form a non-immunized llama comprising at least part of a VHH domain or a complete VHH domain and the size of the phage display library is at least 10^9 and 10^8 pfu/ml. Further, the vector for the phage display library is a modified fd-tet phage and the library is generated as plaques in the absence of tetracycline. The claims are also drawn to a cDNA library comprising nucleotide sequences encoding antigen-binding antibody fragments comprising at least part of a llama VHH domain or a complete llama VHH domain, wherein the cDNA is obtained by isolating lymphocytes from a non-immunized llama, isolating total RNA from the lymphocytes, reverse-transcribing and amplifying the cDNA sequences encoding the antigen-binding antibody fragments, cloning the amplified cDNA into a vector, which is a fd-tet filamentous bacteriophage and recovering the obtained clones. Due to the indefinite nature of claim 25 (see 112, 2nd part e above), part (d) of claim 25 is interpreted to mean that the reverse transcribed cDNA is amplified.

Caterman et al have been described supra.

Casterman et al do not specifically teach phage display libraries of a size of at least 10^9 and 10^8 pfu/ml in claims 5 and 6, or a modified fd-tet phage vector in claim 7,

or the phage display library generated as plaques in the absence of tetracycline in claims 8 and 9, or a cDNA library wherein the vector is fd-tet filamentous bacteriophage in claim 30. These deficiencies are made up for in the teachings of McCafferty et al and Krebber et al.

McCafferty et al teach phage display libraries for the expression of antibodies obtained from a non-immunized animal and the phage may be fd-tet filamentous bacteriophage or a derivative of fd-tet filamentous bacteriophage (see column 16, lines 21-23, 36-42, column 21, lines 2-7, Figure 3 and Example 1).

Krebber et al teach a chloramphenicol resistant (cam^R) and ampicillin resistant (amp^R) fd-tet phage having phage titers of at least 10^9 and 10^8 pfu/ml that were generated as plaques in the absence of tetracycline (see Figure 3b and Table 1). Krebber et al teach that fd-tet phage carrying a tetracycline resistance gene in one of the hairpins of the phage origin of replication, yielded rather low phage titers (see page 228, right column), however, insertion of the ampicillin and chloramphenicol resistant genes individually into the fd-tet vector and selection with the appropriate antibiotic produced highly infective phage and high phage titers (see page 229, left column and Table 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a phage display library of antigen-binding antibody fragments obtained from a non-immunized lama as taught by Casterman et al and to have used fd-tet filamentous bacteriophage (i.e., phage) as taught by McCafferty et al and to have generated the fd-tet phage display library in the

absence of tetracycline for higher phage library titers (i.e., greater than 10^9 pfu/ml) as taught by Krebber et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a phage display library of antigen-binding antibody fragments obtained from a non-immunized lama as taught by Casterman et al and to have used fd-tet filamentous bacteriophage (i.e., phage) as taught by McCafferty et al and to have generated the fd-tet phage display library in the absence of tetracycline for higher phage library titers (i.e., greater than 10^9 pfu/ml) as taught by Krebber et al because Casterman et al teach phage display and cDNA libraries of antigen-binding antibody fragments from a non-immunized lama and McCafferty et al teach fd-tet filamentous bacteriophage for the expression of antibodies obtained from a non-immunized animal and Krebber et al teach that fd-tet phage carrying a tetracycline resistance gene, yielded rather low phage titers, and higher phage titers (i.e., greater than 10^9 and 10^{10} pfu/ml) can be obtained using fd-tet phage generated in the absence of tetracycline. Therefore, it would have been obvious to the skilled artisan to use fd-tet phage generated in the absence of tetracycline in order to increase phage infectivity and produce higher phage titers in the non-immunized lama VHH phage display library taught by Casterman et al. Thus, it would have been obvious to one skilled in the art at the time the invention was made to have produced a phage display library of antigen-binding antibody fragments obtained from a non-immunized lama as taught by Casterman et al and to have used fd-tet filamentous bacteriophage (i.e., phage) as taught by McCafferty et al and to have generated the fd-tet phage

display library in the absence of tetracycline for higher phage library titers (i.e., greater than 10^9 pfu/ml) as taught by Krebber et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

15. Claims 1-9 and 25-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frenken et al [b] (WO 99/37681, 7/29/1999) in view of McCafferty et al (U.S. Patent 6,172,197 B1, filed 6/7/1995) and Krebber et al (FEBS Letters, 377:227-231, 1995).

The claims and their interpretation have been described supra (see item #14 above).

Frenken et al [b] have been described supra.

Frenken et al [b] do not specifically teach phage display libraries of a size of at least 10^9 and 10^8 pfu/ml in claims 5 and 6, or a modified fd-tet phage vector in claim 7, or the phage display library generated as plaques in the absence of tetracycline in claims 8 and 9, or a cDNA library wherein the vector is a fd-tet filamentous bacteriophage in claim 30. These deficiencies are made up for in the teachings of McCafferty et al and Krebber et al.

McCafferty et al have been described supra.

Krebber et al have been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a phage display library of

antigen-binding antibody fragments obtained from a non-immunized lama as taught by Frenken et al [b] and to have used fd-tet filamentous bacteriophage (i.e., phage) as taught by McCafferty et al and to have generated the fd-tet phage display library in the absence of tetracycline for higher phage library titers (i.e., greater than 10^9 pfu/ml) as taught by Krebber et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a phage display library of antigen-binding antibody fragments obtained from a non-immunized lama as taught by Frenken et al [b] and to have used fd-tet filamentous bacteriophage (i.e., phage) as taught by McCafferty et al and to have generated the fd-tet phage display library in the absence of tetracycline for higher phage library titers (i.e., greater than 10^9 pfu/ml) as taught by Krebber et al because Frenken et al [b] teach a phage display library of antigen-binding antibody fragments (and the encoding nucleic acids) comprising at least part of a heavy chain variable domain naturally devoid of light chains (i.e., VHH) obtained from a non-immunized lama and McCafferty et al teach fd-tet filamentous bacteriophage for the expression of antibodies obtained from a non-immunized animal and Krebber et al teach that fd-tet phage carrying a tetracycline resistance gene, yielded rather low phage titers, and higher phage titers (i.e., greater than 10^9 and 10^{10} pfu/ml) can be obtained using fd-tet phage generated in the absence of tetracycline (see Table 1). Therefore, it would have been obvious to the skilled artisan to use fd-tet phage in the absence of tetracycline in order to increase phage infectivity and produce higher phage titers in the non-immunized lama VHH phage display library taught by Frenken et al [b]. Thus, it

would have been obvious to one skilled in the art at the time the invention was made to have produced a phage display library of antigen-binding antibody fragments obtained from a non-immunized lama as taught by Frenken et al [b] and to have used fd-tet filamentous bacteriophage (i.e., phage) as taught by McCafferty et al and to have generated the fd-tet phage display library in the absence of tetracycline for higher phage library titers (i.e., greater than 10^9 pfu/ml) as taught by Krebber et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

16. Claims 1-9 and 25-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoogenboom et al (Immunotechnology 4:1-20, 1998) in view of Lauwereys et al (The EMBO Journal, 17(13):3512-3520, 1998) and Krebber et al (FEBS Letters, 377:227-231, 1995).

The claims and their interpretation have been described supra (see item #14 above).

Hoogenboom et al teach phage display antibody libraries from non-immunized animal sources, such as the V-genes from lymphoid cells to create a naïve repertoire of rearranged genes (see page 5, right column, in particular). Hoogenboom et al teach that antigen-biased IgG V-genes should be avoided (see page 5, right column, in particular). Hoogenboom et al teach cDNA libraries encoding antibodies from a non-immunized animal source comprising the steps of isolating lymphocytes, isolating RNA for the lymphocytes, synthesizing cDNA and amplifying the cDNA by PCR, cloning the

amplified cDNA into a vector and recovering the obtained clones (see pages 5-6 and Figure 3, in particular). Hoogenboom et al also teach the fd-tet vector (see page 3, left column, in particular). Additionally, Hoogenboom et al teach the construction of an antibody phage library following immunization of a camel, however, Hooogenboom et al admits that immunization is not always possible due to ethical constraints, neither always effective due to tolerance mechanisms towards or toxicity of antigen (see page 5, left column, in particular). Hoogenboom et al teach that phage display libraries of naïve antibodies that are sufficiently large and diverse can be used to generate antibodies to a large panel of antigens, including self, non-immunogenic and toxic antigens (see page 6, left column, in particular). Hoogenboom et al do not specifically teach a cDNA antibody library or phage display library of antigen-binding antibody fragments obtained from a non-immunized llama comprising at least part of a VHH domain or a complete VHH domain and the size of the phage display library is at least 10^9 and 10^8 pfu/ml or a fd-tet phage display library generated in the absence of tetracycline. These deficiencies are made up for in the teachings of Lauwereys et al and Krebber et al.

Lauwereys et al teach that heavy chain antibodies devoid of light chains (i.e., VHH) can be obtained from llamas and these heavy chain antibodies have acquired the potential to recognize protein cavities and as such the ability to inhibit enzymes (see page 3512, right column, in particular). Lauwereys et al teach that VHH antibodies posses superior properties such as simple isolation, high solubility and stability and are advantageous for intracellular immunization (see page 3518, left and right columns, in

particular). Lauwereys et al teach the single-domain nature of the VHH antibodies avoids the introduction of essential linkers used in scFv constructs, which might lead to aggregation or susceptibility to proteolysis and it is likely that VHH antibodies are more feasible for intracellular immunization compared to conventional scFvs due to their superior enzyme-neutralizing capacity (see page 3518, right column, in particular).

Krebber et al have been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a phage display library of VHH antibodies as potent enzyme inhibitors as taught by Lauwereys et al and to have obtained the VHH antibodies from a non-immunized lama since immunization is not always ethically possible, nor always effective for non-immunogneic and toxic antigens as taught by Hoogenboom et al and it would have been obvious to have used fd-tet phage in the absence of tetracycline for higher phage library titers (i.e., greater than 10^9 pfu/ml) as taught by Krebber et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a phage display library of VHH antibodies as potent enzyme inhibitors as taught by Lauwereys et al and to have obtained the VHH antibodies from a non-immunized lama since immunization is not always ethically possible, nor always effective for non-immunogneic and toxic antigens as taught by Hoogenboom et al and it would have been obvious to have used fd-tet phage in the absence of tetracycline for higher phage library titers (i.e., greater than 10^9 pfu/ml) as taught by Krebber et al because Hoogenboom et al teach al teach cDNA

libraries and phage display libraries of antibodies from non-immunized animal sources and immunized sources are not always ethically possible, neither always effective due to tolerance mechanisms towards or toxicity of antigen and phage display libraries of naïve antibodies that are sufficiently large and diverse can be used to generate antibodies to a large panel of antigens, including self, non-immunogenic and toxic antigens and Lauwereys et al teach that VHH antibodies obtained from llamas are potent enzyme inhibitors and are better suited for intracellular immunization compared to conventional scFvs due to their superior enzyme-neutralizing capacity. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a phage display library of VHH antibodies as potent enzyme inhibitors as taught by Lauwereys et al and to have obtained the VHH antibodies from a non-immunized lama since immunization is not always ethically possible, nor always effective for non-immunogneic and toxic antigens as taught by Hoogenboom et al and it would have been obvious to have used fd-tet phage in the absence of tetracycline for higher phage library titers (i.e., greater than 10^9 pfu/ml) as taught by Krebber et al because Hoogenboom et al and Krebber et al teach fd-tet phage and Krebber et al teach that fd-tet phage carrying a tetracycline resistance gene, yielded rather low phage titers, and higher phage titers (i.e., greater than 10^9 and 10^{10} pfu/ml) can be obtained using fd-tet phage generated in the absence of tetracycline (see table 1). Therefore, it would have been obvious to the skilled artisan to generate a phage display library in the absence of tetracycline to obtain higher phage titers because phage display libraries of naïve antibodies that are sufficiently large and

diverse can be used to generate antibodies to a large panel of antigens, including self, non-immunogenic and toxic antigens. Further, it would have been obvious to by-pass immunization since immunized sources are not always ethically possible, nor always effective towards non-immunogenic and toxic antigens. Thus, it would have been obvious to one skilled in the art to at the time the invention was made to have produced a phage display library of VHH antibodies as potent enzyme inhibitors as taught by Lauwereys et al and to have obtained the VHH antibodies from a non-immunized lama since immunization is not always ethically possible, nor always effective for non-immunogneic and toxic antigens as taught by Hoogenboom et al and it would have been obvious to have used fd-tet phage in the absence of tetracycline for higher phage library titers (i.e., greater than 10^9 pfu/ml) as taught by Krebber et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at (571) 272-0827 from 8:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (571) 272-0841.

Official papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The official fax number for Group 1600 where this application or proceeding is assigned is (703) 872-9306.

Respectfully,
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